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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/630,383	04/10/96	POULETTY	P A-55320-2/BI

EXAMINER

18M1/0701

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3/31/97

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-13 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-13 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

PTOL-326

15. Claims 1-13 are under consideration. Claims 1-3,6,8,10,11 have been amended.

RESPONSE TO APPLICANTS ARGUMENTS

16. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).
Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-3,5-8 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending application Serial No. 07/690,530 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

18. Claim 4 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,4 and 5 of copending application Serial No. 07/690,530 in view of prior art disclosed in the specification (page 9, first paragraph) for

the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

19. Claim 12 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-8 of copending application Serial No 07/690530 in view of Lorberboum-Galski et al. for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

20. Claims 9-11 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,4,5 of copending application Serial No. 07/690,530 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

21. Claims 1-3,5-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9 and 10 of copending application Serial No. 07/690,530 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

22. Claim 12 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9 and 10 of copending application Serial No. 07/690,530 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

23. Claims 9-11 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-8 of copending application Serial No. 07/690,530 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

24. Claims 1-13 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7,11,12 of copending

application Serial No. 08/254299 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

25. Claims 1-8,12,13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-10 of copending application Serial No. 08/254299 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

26. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

27. Claims 9-11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 8-10 of copending Application No. 08/254,299 for the reasons elaborated in the previous Office Action. Applicant has indicated that the instant rejection will addressed at a later date.

28. Claims 1-13 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in paragraph 30 of the previous Office action. Applicants arguments have been considered and deemed not persuasive.

The specification does not disclose how to use the instant invention for the treatment of disease in vivo in humans. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986. Regarding applicants comments on pages 3-15 of the amendment filed 3/31/97, the following comments are made. Regarding applicants various comments about utility and the utility guidelines, applicant is reminded that no rejection under 35 U.S.C. §101 is present in the instant Office Action and that the rejection under consideration is under 35 U.S.C. § 112, first paragraph. The Official Gazette (1177 OG 146) states in column 1, third paragraph (under section I) that lack of a rejection under 35 U.S.C. §101 does not mean that a specification is therefore enabled under 35 U.S.C. §112, first paragraph. The claims of the instant invention read on a method that the specification discloses can be used for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy. The state of the art is such that is unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of disease in vivo in humans.

Regarding the mouse data disclosed in page 23 of the specification, said experiments relate to the lysis of normal cells and provides no evidence that the instant invention can be used for the treatment of any mouse disease. Regarding the mouse allograft data disclosed in page 30 of the specification, it is well known in the art that rodent models for the study of transplantation do not produce results that are readily applicable to humans and are therefore not predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans (see page 100, first full paragraph). Tueveson et al. also teach that, "However, today's small animal models seem to be insufficient to produce data for clinical decision-making." (page 101, second paragraph). Osband et al. teaches that the response of animals to immunotherapy is not predictive of the response in humans(see page 193, second column, first paragraph). The data disclosed in page 30 of the specification provides no evidence that naturally occurring endogenous antibodies (eg. autoantibodies, antibodies against xenoantigens), which are encompassed by the claims of the instant invention, can function as an effector mechanism in the claimed invention.

Borrebaeck et al. teach that naturally occurring antibodies against xenoantigens(eg. anti α gal antibodies) do not function as an endogenous effector system as per the claimed method, for the reasons stated below (see comments about Borrebaeck et al.). The evidence of record has also provided no working examples demonstrating that the conjugates used in the method of the instant invention can used to reduce the concentration of a soluble target molecule.

Regarding the Soulillou declaration filed 3/31/97, no copy of Soulillou's curriculum vitae was submitted with the instant declaration, therefore, it is unclear as to whether Dr. Soulillou is an expert in the field of immunology. Furthermore, the Soulillou declaration provides no experimental evidence which establishes that the rodent models for the study of transplantation produce results that are readily applicable to humans and are therefore predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans. The Soulillou declaration filed 3/31/97 does not provide any evidence that contradicts the aforementioned problem noted by Tueveson with regards to rodent models for transplantation. In fact, Soulillou seems to indicate that Tuevson et al. are correct in stating that there is no direct correlation between the rodent model and applicability to human use (eg. see first complete paragraph). The issue at hand is not whether the rodent model is used to screen for immunosuppressive drugs, but whether the rodent model is predictive in itself of whether an agent can be used in vivo for the treatment of human disease. Regarding Soulillou's comments on page 2, the murine and human immune systems differ in many ways. For example, the human immune system contains anti- α gal antibodies are not found in rodents and which can neutralize the efficacy of rodent antibodies. Regarding applicants comments about the Tuevson et al. publication, no actual evidence has been presented in the Soulillou declaration which refutes the statements made by Tuevson et al. Regarding comments in the Soulillou declaration about Borrebaeck et al., Borrebaeck et al. teach that murine antibodies often contain the α gal antigen (see page 477). Borrebaeck et al. teach that naturally occurring anti- α gal antibodies are found in humans and that said antibodies bind murine monoclonal antibodies when said murine monoclonal antibodies are administered to humans (see page 477, third column first complete paragraph). Borrebaeck et al. teach that , "The presence of anti-Gal antibodies in human serum

ensures a quick removal of the xenogeneic mouse mAbs, containing Galα 1-3Gal residues, which results in a lack of antibody mediated effect on neoplastic target cells"(see page 477, third column first complete paragraph). It appears that conjugates containing α gal antigen would also suffer a similar fate and therefore also not be available to mediate lysis of a target cell. Borrebaeck et al. also teaches that the binding of anti-α gal antibodies interferes with the immune function of murine monoclonal antibodies without resulting in any effector function as a consequence of the bound anti-α gal antibodies (see page 477, third column, first complete paragraph, last sentence). The teachings of Borrebaeck et al. seem to indicate that the preformed antibodies (eg. endogenous antibodies) do not act as an immunologic effector system upon binding of said antibodies to an exogenously administered agent , but instead result in the removal of said agent thus preventing the agent from reaching the appropriate target cell. The Soulillou declaration has provided no actual evidence that contradicts the statement made by Borrebaeck et al.

With regards to the in vivo use of antibody containing conjugates, Waldmann teaches that the therapeutic use of antibody treatment with any particular antibody/antibody conjugate in humans is unpredictable from in vitro data or in vivo animal data alone. Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). Waldmann also states that results from clinical studies in humans using antibody based therapeutics for the treatment of cancer did not fulfill the hopes engendered by in vitro studies (see page 1660, second column, last paragraph). Waldmann teaches that the effectiveness of rodent monoclonal antibodies is limited because they "have a short survival time in humans and induce an immune response that neutralizes their therapeutic effect"(page 1658, second column, third paragraph). Waldmann teaches that even human antibodies can be immunogenic by virtue of their idiotypic elements(see page 1659, first column, lines 4 and 5). Harris et al. teach that, "There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy" and goes on to list problems encountered upon the use of murine antibodies for human therapy (see page 42, second column, first paragraph). Harris et al. also states that, "However, the residual HAMA response to chimaeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective" (see page 42, third column). The Soulillou declaration has provided no actual evidence that contradicts the statement made by Waldmann or Harris et al. Regarding

applicants comments on page 12 of the instant amendment, none of the claims under consideration recite the use of humanized monoclonal antibodies or that the host is immunosuppressed. No evidence has been presented indicating that murine monoclonal antibodies per se can be used for the treatment of human disease.

Regarding applicants comments on page 14 of the instant amendment, the claims of the instant invention do not specify that the target is T cells involved in transplantation rejection. The claims read on a method where the target could be a T cell lymphoma which expresses IL-2 receptors. In such a scenario, normal T cells capable of mediating killing would also express the IL-2 receptor, and therefore the aforementioned conjugate would bind to normal T cells and not be available to bind a target cell. Furthermore, the killing of normal T cells would leave tumor bearing patient immunocompromised without necessarily having any effect on the T cell lymphoma. This would also apply to many cytokines, whose receptors are also found on T cells (such as IL-4, IL-6, IL-10, etc.).It is unclear as to how the method of the instant invention can inactivate target cells without also inactivating normal cells that express receptors for said cytokine. If the target cell population is present in lesser numbers compared to normal cells which express the relevant cytokine receptor it is also unclear as to whether sufficient quantities of said conjugate would be present to react with a target cell population after interaction with normal cells that possess the pertinent cytokine receptor.

With regards to claims that read on the use of α gal containing conjugates in mammals, anti-α gal endogenous antibodies are not found in mammals per se, but only in humans and old world monkeys (see Borrebaeck et al., column 1, first indented paragraph). Therefore said conjugates could not be used in mammals per se.

In addition, there is no guidance in the specification as to how to determine the dosage of conjugate to use for treatment of a particular disease. It is therefore unclear as to whether the dosages used in said experiment could be used for the treatment of disease, because no disease was actually treated in said experiment. There is also no evidence of record that establishes that the mouse pharmacokinetic response to the conjugate would be the same as humans. Borrebaeck et al. establish that there are clear pharmacokinetic differences in the halflife of murine antibodies administered to mice versus humans, in that murine antibodies administered to humans have greatly reduced halflife in comparison to human antibodies (see column 1, page 477). Therefore a xenogeneic conjugate administered to a human would not necessarily have the same

pharmacokinetic properties as when said conjugate was administered to a human. The Borrebaeck et al. reference establishes that conjugates containing α gal would be subjected to an anti-α gal response (that can neutralize the conjugate), wherein such a response would not occur in mice because anti-α gal antibodies are not found in mice. There is also no guidance in the specification as to how to determine if an appropriate level of endogenous antibody (eg. endogenous cytotoxic effector) is present so that target cell lysis could be effected by the administered conjugate.

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims 1,5 and 6 remain rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Segal et al (US Patent 4,676,980) as evidenced by Roitt and Rosen et al. for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Regarding amended claim 1, Segal et al. teach that immunoglobulin fragments (eg. Fab or F(ab')2 can be used in place of antibodies in the claimed invention (see column 4, second paragraph). Claim 1 recites that the moiety is "other than an antibody". Fab or F(ab')2 are not antibodies, they are antibody fragments because they lack portions of the intact antibody molecule. The claim under consideration does not exclude the use of antibody fragments in the conjugate used in the claimed method and therefore is anticipated by Segal et al. It appears that this rejection was erroneously withdrawn in parent case 07/690530.

31. Claims 1-6,12 stand rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Pouletty (EP 0510949) for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments on page 17 of the instant amendment, Pouletty (EP

0510949) can be a reference under 35 U.S.C. § 102(b), while the identical disclosure does not provide priority for the instant application because said reference anticipates a particular species recited in a claim or encompassed in the claims without providing support for the scope of the particular genus or other species recited in said claim.

Regarding claim 1, the scope of amended claim 1 is not disclosed in parent application 07/690530. Regarding applicants comments about parent application 07/690530, page 4, line 7, said sentence recites "ligands for receptors", not ligands per se. The scope of claim 1 is broader than the scope of "ligands for receptors" because there is no limitation in proviso (b) of claim 1 which recites that the ligand is for a receptor. Regarding claim 2, application 07/690530, page 5, line 1 does not disclose an "an antigen foreign to said mammalian host to which antibodies are present" or provide support for the scope of such a claim. Said language encompasses the use of xenoantigens per se, but the use of xenoantigens is not disclosed in application 07/690530. Regarding claim 6, there is no disclosure in parent application 07/690530 of "low molecular weight binding molecule, wherein said molecular weight is between about 100 to about 5000 daltons". Regarding applicants comments about claim 3, the SEB of claim 3 is not disclosed in parent application 07/690530. There is no evidence of record that establishes that SBB is intended to refer to SEB. Regarding claim 12, page 4 of parent application 07/690530, does not teach "an immunoglobulin fragment specific for a surface membrane protein of a T cell".

32. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

33. Claim 4 remains rejected under 35 U.S.C. § 103 as being unpatentable over Pouletty (EP 0510949) in view of prior art disclosed in the specification (page 9, first complete paragraph) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive. Regarding applicants arguments, while the claimed invention is obvious over the prior art, there is no disclosure of said invention in parent case 07/690530, thus, said invention does not receive priority to said application.

OTHER REJECTIONS

34. The following new grounds of rejection were necessitated by applicants amendment.

35. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "an antigen foreign to said mammalian host to which antibodies are present" in claim 2. Regarding applicants comments about the specification, page 8, lines 1-5, the scope of claim 2 is not disclosed in said passage of the specification.

36. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of the method of claim 6. The specification, page 6, lines 23-25 disclose small organic molecules with a molecular weight recited in said claim, not "low molecular weight binding molecule" with the

molecular weight recited in said claim.

37. No claim is allowed.

38. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

39. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7939.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00.
The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Serial No. 08/630383
Art Unit 1816

RONALD B. SCHWADRON
PRIMARY EXAMINER
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